EXHIBIT A151

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Morbidity and Mortality in Talc-Exposed Workers

Ebba Wergeland, MD, MSc, Aage Andersen, MD, and Anders Bærheim, MD

Cancer incidence and cause-specific mortality were studied in a male cohort of 94 talc miners and 295 talc millers, exposed to non-asbestiform talc with low quartz content. No excess risk was found compared with national age-specific incidence. Six cases of lung cancer occurred versus 6.49 expected (miners: observed 2, expected 1.27; millers: observed 4, expected 5.22). There were 3 deaths due to non-malignant respiratory disease against 10.9 expected (miners: observed 1, expected 2.5; millers: observed 2, expected 8.4). Mesothelioma, tuberculosis, or pneumoconiosis were not recorded as causes of death. Pneumoconiosis was noted as a contributory cause in three cases (silicosis two, talcosis one). Further follow-up will reduce any potential impact of "healthy worker" selection.

Key words: cancer, respiratory disease, pneumoconiosis, non-asbestiform talc, quartz

INTRODUCTION

Talc is a layer-type sheet magnesium silicate that commonly occurs in nature contaminated with varying amounts of other minerals such as magnesite, dolomite, tremolite, anthophyllite, chlorite, and quartz.

Excess mortality from cancer and non-malignant respiratory diseases has been reported in talc miners and millers. In several studies the talc contained considerable amounts of anthophyllite and tremolite [Kleinfeld et al., 1974; Dement et al., 1980; Stille and Tabershaw, 1982]. However, Rubino et al. [1976, 1979], Selevan et al. [1979], and Lephonte et al. [1983] have reported excess mortality from non-malignant respiratory diseases after exposure to talc with low asbestos content (non-asbestiform talc). Contrary to other studies, Selevan et al. [1979] and Katsnelson and Mokrosonova [1979] showed excess mortality from respiratory cancer (and from gastrointestinal cancer in the latter study). Thomas and Stewart [1987] found excess mortality from respiratory cancer in workers exposed to a mixture of silica and non-asbestiform talc in the manufacture of ceramic plumbing fixtures. They suggest talc as an etiological factor, with silica as a possible co-carcinogen or promoter.

Directorate of Labour Inspection, Oslo, Norway (E.W.).
The Cancer Registry of Norway, Montebello, Oslo, Norway (A.A.).
A/S Norwegian Talc, Knarrevik Talc Mill, Knarrevik, Norway (A.B.).
Address reprint requests to Dr. Ebba Wergeland, Department of Preventive Medicine, Oslo University, Gydas vei 8, Oslo 3, Norway.
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TABLE I. Number of Subjects Included in the Study Cohort, From Altermark Talc Mine and Knarrevik Talc Mill, Norway

	Mine	Mill
All employees (in 1981) since 1944 (mine) or 1935 (mill)	117	332
Excluded due to:		
employment after 1972	14	27
employment < 1 year (mine) or < 2 years (mill) or in non-exposed job	9	10
Total study cohort	94	295
Number of deaths 1953–1987	27	90
Number of person-years	2,326	7,677

Norwegian talc contains only trace amounts of quartz, tremolite, and anthophyllite. Fibers have been detected in quantities near the detection limit for optical microscopy [Fristedt et al., 1968; Parkes, 1982]. The low fiber content has also been confirmed by electron microscopic analysis (Bjørn Gylseth, Institute of Occupational Health, personal communication). Radiographic readings indicating pulmonary fibrosis have been reported after exposure to Norwegian talc in nine talc mill workers and one talc saw-mill worker [Bruusgaard and Skjelbred-Knudsen, 1948], five workers in the rubber industry [Fristedt et al., 1968], and one worker who had been employed in a soapstone mine and a talc mill [Berner et al., 1981]. The lungs of this latter patient were analyzed for mineral content by electron microscopy and x-ray diffractometry. Talc was the main mineral component. Quartz and asbestos were not detected in the lung ash.

The aim of the present study was to investigate if excess cancer risk or excess mortality from respiratory diseases could be demonstrated after exposure to Norwegian high purity talc. Four talc mills and four talc mines were operating in Norway when the study was initiated. However, adequate information was only available from one mine and one mill.

MATERIALS AND METHODS

The study comprised 389 men, 94 from the mine and 295 from the mill (Table I). All employees from the mine in the years 1944–1972 with at least 1 year of employment in talc-exposed jobs and all employees from the mill in the years 1935–1972 with at least 2 years of employment in talc-exposed jobs were included.

Operations at Altermark Talc Mine in northern Norway began in 1932. The main minerals in the talc deposit are talc and magnesite. In addition, the ore contains small amounts of magnetite, chromite, chlorite, and serpentine (antigorite). The adjacent rocks contain serpentine, mica, feldspar, calcite, and amphiboles (hornblende, tremolite) (Bjørn Gylseth, Institute of Occupational Health, personal communication). The maximum number of employees was 50; at the time of the study in 1981, there were 20.

TABLE II. Number of Talc Miners and Millers in the Three Exposure Categories*

	Dust exposure level				
	1	2	3	?	Total
Miners					
Years employed					
1(2)–5	16	28	3	0	47
6–15	4	12	8	1	25
16+	7	10	5	0	22
Total	27	50	16	1	94
Millers					
Years employed					
1(2)–5	11	12	9	33	66
6–15	19	47	21	8	95
16+	15	69	50	0	134
Total	45	129	80	41	295

*Level of talc dust exposure (subjective assessment) by total duration of employment in exposed work. (Low = 1, medium = 2, high = 3, unknown = ?).

Knarrevik Talc Mill in western Norway started operation in 1935. At the time of the study (1982), there were 85 employees. Around 90% of the raw material for Knarrevik comes from Altermark Talc Mine, and the rest comes from India. In addition to talc, dolomite and mica are also ground.

Information about the miners was gathered from company pay rolls, lists of union membership, and the central registry of silica-exposed workers of the National Board of Occupational Safety and Health. Information about the millers was gathered from the company protocol, in which every new employee had been registered since the mill opened. No additional subjects were found in the files of the local occupational health service or in the central registry of silica-exposed workers of the National Board for Occupational Safety and Health. The information included name, date of birth, first and last date of employment, and number of periods of employment. The majority of miners and millers could be classified according to degree of individual dust exposure (categories 1–3), based on a subjective assessment by colleagues (Table II).

For the miners, information about smoking habits was gathered simultaneously (in 1981) and was available for 63 of the 94 miners. Of these, the proportion of smokers was 76% (48), non-smokers 8% (5), and former smokers 16% (10). No information was available on smoking habits for the millers.

The individuals were considered at risk from January 1, 1953 [or mid-year of first employment plus 1 year (mine) or 2 years (mill), if later] until December 31, 1987 (or date of death). Each individual alive at the 1960 census, or born later, has a personal identification number in the registry of the Central Bureau of Statistics of Norway. Matching of deaths and cancer cases was thereby fully computerized after 1960, but had to be done manually for the preceding years.

The study compares observed and expected numbers of cause-specific mortality and cancer morbidity. Information on date and main cause of death was obtained from the death certificate registry of the Central Bureau of Statistics. Information on cancer

TABLE III. Causes of Death Among Workers Exposed to Norwegian Talc*

	Mine		Mill		Total			
Cause of Death (ICD 7)	Obs	Exp	Obs	Exp	Obs	Exp	SMR	95% CI
All causes	27	32.9	90	122.3	117	155.2	75	62–89
All malignant neoplasms (140–207)	9	6.9	17	27.3	26	34.2	76	50–111
Diseases of the circulatory system (400–468)	11	16.7	57	62.2	68	78.9	86	67–110
Ischemic heart disease (420–422)	7	10.6	37	41.0	44	51.6	85	62–114
Diseases of the respiratory system (470–527)	1	2.5	2	8.4	3	10.9	28	6–80
Accidents, poisoning, and violence (800–999)	0	1.9	3	6.7	3	8.6	35	7–102
Other known causes	6[a]	4.9	11	17.7	17	22.6	75	35–120

*Observed (Obs) and expected (Exp) number of deaths 1953–1987. SMR, standardized mortality ratio; 95% CI, 95% confidence interval.
[a]Four of six were coded sudden death (ICD 795).

cases was provided by the Cancer Registry. The registration of all new cases is considered complete from 1953, with compulsory reporting from hospital departments and histopathological laboratories. For estimation of the expected number of cause-specific deaths, and expected number of new cancer cases, our study used the 5-year age-specific mortality and incidence rates for each of the years 1953–1987 as recorded in the same registries for the total male Norwegian population.

The level of dust exposure was not registered during the actual period (before 1972). Samples were collected in 1980–1982 and analyzed at the Institute of Occupational Health in Oslo. Total dust levels, by personal sampling, varied greatly by job category and workplace (mine: 0.94–97.35 mg/m^3; mill: 1.4–54.1 mg/m^3), with peak exposures in the mine by drilling (318.9 mg/mm^3) and in the mill by working in the storehouse (109 mg/m^3). By optical microscopic analysis of air samples, the fiber concentration varied from less than 0.2 up to 0.9 fibers/ml. The number of fibers per unit weight of dust was not determined. The fibers were identified by electron microscopy and comprised tremolite, antophyllite, and talc particles fulfilling the fiber definition, i.e., length-to-diameter ratio greater than 3:1. Dust samples from both the mine and the mill contained less than 1% quartz as analyzed by x-ray diffractometry.

Information about radon daughter exposure was provided by the Institute of Mining, Trondheim (Tom Myran, personal communication). Mean value for radon daughter concentrations in the Altermark mine was 3.5 pCi/l at the worksite, with a range of 1.5–7.5 pCi/l. (100 pCi = 1 working level.)

RESULTS

Mortality

The standardized mortality ratio (SMR) was 75, with 117 observed deaths and 155.2 expected (Table III). The miners comprised 24% of the total cohort (Table I). The total number of deaths in the mine was 27 with 32.9 expected; in the mill, 90 with

TABLE IV. Cancer Incidence Among Millers and Miners Exposed to Talc in Norway*

	Mine		Mill		Total			
Primary site (ICD 7)	Obs	Exp	Obs	Exp	Obs	Exp	SIR	95% CI
All sites (140–207)	15	10.72	31	40.60	46	51.32	90	66–120
Bladder (181)	0	0.67	7	2.68	7	3.35	209	84–431
Stomach (151)	3	1.19	3	4.24	6	5.43	110	41–215
Kidney (180)	0	0.38	2	1.49	2	1.87	107	13–386
Lung (162)	2	1.27	4	5.22	6	6.49	92	34–201
Prostate (177)	4	1.96	3	7.33	7	9.29	75	30–155
Intestine (152–154)	1	1.39	4	5.37	5	6.76	74	24–173
Other sites[a]	5	3.86	8	14.27	13	18.13	72	38–123

*Observed (Obs) and expected (Exp) number of new cancer cases 1953–1987. SIR, standardized incidence ratio; 95% CI, 95% confidence interval.
[a]Mine: brain (1), lymphoma (1), eye (1), lip (1), unknown site (1); mill: tongue (1), malignant melanoma (2), liver (1), leukemia (1), unknown site (1), non-melanoma skin cancer (2).

122.3 expected. In the mine, a higher than expected number of deaths occurred for all cancers combined (9 observed, 6.9 expected).

Morbidity

During the follow-up period, 46 cases of cancer were observed against 51.32 expected. Results are given in Table IV for selected cancers, ranked according to standardized incidence ratio (SIR). A higher than expected number of cases occurred for all cancers combined in the mine (15 observed against 10.72 expected), but not in the mill (31 observed, 40.60 expected). The excess number of cases in the mine was confined to cancer of the stomach (3 observed, 1.19 expected), cancer of the prostate (4 observed, 1.96 expected), and lung cancer (2 observed, 1.27 expected). In the mill, a higher number than expected was seen for cancer of the bladder (7 vs. 2.68) and kidney (2 vs. 1.49). For lung cancer no excess incidence could be demonstrated (4 observed, 5.37 expected).

DISCUSSION

Total Mortality

In both the talc miners and the millers, total mortality was lower than expected. The total mortality rate in the counties where the companies are situated is approximately the same as the national rate; thus the low mortality cannot be explained by geographical variation.

Low mortality is normal in occupational cohorts compared with the total population, which also includes individuals unfit for work [Fox and Collier, 1976]. In physically demanding jobs such as mining and milling, a positive selection into the occupational group (healthy population effect) and a negative selection out (survivor population effect) tends to occur. As our cohort excludes those employed for less than 1 year, both effects must be expected, but with decreasing impact as follow-up time increases.

Our findings are not in accordance with Rubino et al. [1979] and Selevan et al. [1979], who found excess total mortality in talc millers and miners, mainly due to non-malignant respiratory diseases.

Cause-Specific Mortality

There were fewer deaths than expected from non-malignant respiratory diseases. However, the numbers are too small for further conclusions. The effects of selection may be particularily pronounced for respiratory diseases, as observed by Fox and Collier [1976]. Contrary to our findings, Rubino et al. [1979], Selevan et al. [1979], Lephonte et al. [1983], and Thomas and Stewart [1987] found increased mortality due to non-malignant respiratory diseases. Lephonte et al.'s [1983] results were only published as a short communication and are therefore difficult to evaluate. Thomas and Stewart [1987] explain the excess mortality by the concomitant high exposure to silica. In the Rubino et al. [1979] study, the miners, in particular, had excess mortality from pneumoconiosis and pulmonary tuberculosis. Although the talc was relatively free from quartz, the quartz content measured in dust from drilling operations was up to 18%. Only one death from pneumoconiosis occurred where non-asbestiform talc with less than 2% quartz was the only known exposure. The study by Selevan et al. [1979] is the only one in which excess mortality from respiratory diseases seems to result from high purity talc exposure alone [Boundy et al., 1979]. There were 11 deaths (expected 1.79) from non-malignant respiratory diseases (pneumonia and influenza excluded). Radiographic evidence of pneumoconiosis had been recorded for 9 of the 11, but it is not known whether pneumoconiosis was actually a cause of death. The excess was marked only in millers, and was not observable before 15 years after first employment.

Non-malignant respiratory disease was listed in the death certificate registry as cause of death on one miner and two millers in our study. The diagnosis was pneumonia in all three cases.

Copies of all death certificates except two were available; consistent with the information already provided by the death certificate registry, we found no kind of pneumoconiosis recorded as the main cause of death.

Pneumonia was recorded as a contributory cause of death in one case, the principal cause being septicaemia. Silicosis was recorded twice (one miner, one miller) and talcosis once (one miller) as a contributory cause of death, the principal cause being myocardial infarction, mors subita, and pneumonia, respectively. Pneumoconiosis is commonly induced only after a long latency period. However, 85% of all subjects in the present study have a follow-up time since first employment of 20 years or more. The three observed cases of death from nonmalignant respiratory disease occurred in this subgroup.

The proportion of ever smokers was high (92%) among the subjects (miners) for whom information was available. Different smoking patterns can therefore hardly explain the low respiratory disease mortality seen in this study, compared with the Selevan et al. [1979] study.

Differences in dust exposure levels might explain the difference. However, at least 25% of our cohort belongs to the highest exposure category (Table II).

The low mortality from non-malignant respiratory disease is apparently also in contradiction to the reports of pulmonary fibrosis after exposure to Norwegian talc [Bruusgaard and Skjeldbred-Knudsen, 1948; Fristedt et al., 1968; Berner et al., 1981]. However, in the majority of these cases, the x-ray changes were not accompanied by any significant loss of lung function. Bruusgaard [1948] recalls how one of the patients with the most prominent x-ray changes (described as silicatosis of stage

TABLE V. Cancer Incidence Among Millers and Miners Exposed to Talc in Norway by Years Employed*

	Years employed					
	1–4		5–19		20+	
Primary site (ICD 7)	Obs	Exp	Obs	Exp	Obs	Exp
All sites (140–207)	11	9.60	19	24.45	16	17.27
Bladder (181)	1	0.58	5	1.51	1	1.24
Kidney (180)	1	0.36	1	0.87	0	0.64
Stomach (151)	2	1.00	2	2.78	2	1.65
Lung (162)	0	1.23	3	2.91	3	2.35
Prostate (177)	1	1.38	3	4.45	3	3.36
Intestine (152–154)	1	1.24	1	3.17	3	2.35
Other sites	5	3.81	4	8.76	4	5.68

*Observed (Obs) and expected (Exp) number of new cancer cases 1953–1987.

II–III without reference to classification system) did very well in a fatiguing cross-country ski competition. The low mortality from respiratory diseases may therefore reflect a lack of agreement between pulmonary changes induced by Norwegian high purity talc (and detectable by x-ray) and functional loss. Of the three cases for which pneumoconiosis was noted on the death certificates in this study, only one actually died from a respiratory disease (pneumonia).

The mortality from non-malignant respiratory disease may increase with further follow-up time, as any impact of "healthy worker" selection becomes less prominent.

In the present study, the probability of detecting an increased mortality from non-malignant respiratory diseases ($\alpha = 0.05$, one-sided) is 83% for a true relative risk (RR) = 2.0 and 100% for RR = 3.0, assuming a Poisson distribution.

Cancer Incidence

The higher cancer incidence among the miners was not greater than might be due to random variation. For the mill, the total cancer incidence was lower than expected. In both groups the numbers are too small to form inferences on particular cancer types. As talc from the mine was the main raw material for the mill, the numbers from both mine and mill have been summed to assess an eventual cancer risk from the talc. The present study shows no excess of lung cancer.

A total of six new cases of cancer was observed in the subgroup belonging to the highest exposure (3) category (Table II). The expected number was 13.55. There were no cases of cancer of the lung in this subgroup.

A total of 16 new cases of cancer was observed in the subgroup with more than 20 years of talc exposure (17.27 expected). There were 3 cases of lung cancer (2.35 expected) (Table V).

In the subgroup with more than 20 years since first employment, the total number of new cases of cancer was 40 (37.07 expected). The observed number of cases of stomach cancer was 5 (3.63 expected), cancer of the intestines 5 (5.07 expected), and lung cancer 4 (4.74 expected) (Table VI).

Rubino et al. [1976, 1979] and Lephonte et al. [1983] found no excess cancer incidence in workers exposed to non-asbestiform talc. Katsnelson and Mikrosonova

TABLE VI. Cancer Incidence Among Miners and Millers Exposed to Talc in Norway by Years Since First Exposure*

	Years since first exposure					
	1–19		20–29		30+	
Primary site (ICD 7)	Obs	Exp	Obs	Exp	Obs	Exp
All sites (140–207)	6	14.25	18	16.24	22	20.83
Bladder (181)	1	0.76	6	1.02	0	1.57
Kidney (180)	0	0.55	0	0.59	2	0.73
Stomach (151)	1	1.80	2	1.82	3	1.81
Lung (162)	2	1.75	1	2.01	3	2.73
Prostate (177)	1	1.80	2	3.00	4	4.49
Intestine (152–154)	0	1.69	2	2.15	3	2.92
Other sites	1	5.90	5	5.65	7	6.58

*Observed (Obs) and expected (Exp) number of new cancer cases 1953–1987.

[1979] reported excess incidence of both lung cancer and gastric cancer. However, mortality rates were calculated in a way that makes it difficult to evaluate the study. Thomas and Stewart [1987] found excess mortality from lung cancer in workers exposed to high levels of silica with or without concomitant exposure to non-fibrous talc. The excess was observable in the subgroups with silica exposure alone and with silica and fibrous talc combined but was statistically significant only with combined exposure to silica and non-fibrous talc. There was also a dose–response relationship between lung cancer mortality and duration of exposure for talc, but not for silica. According to the authors, data suggest that non-fibrous talc is associated with increased lung cancer risk. An alternative interpretation of the same data would be that silica exposure is the main etiological factor. Association between silica exposure and lung cancer has been suggested by others [Goldsmith et al., 1982]. In a recent review of available data [IARC, 1987], an IARC working group found sufficient evidence for carcinogenicity of crystalline silica to experimental animals, and limited evidence for carcinogenicity to humans. They found inadequate evidence for carcinogenicity of talc to either experimental animals or humans. Both the absence of excess lung cancer mortality in the present study of workers exposed to talc with low quartz content, and the excess found by Thomas and Stewart in workers exposed to talc with high quartz content, are compatible with these evaluations.

Selevan et al. [1979] reported 5 cases of lung cancer in miners against 1.15 expected. The authors consider that this excess must be due to causes other than talc, for instance to radon daughter exposure, as no similar excess was found among the presumably more exposed millers. The radon daughter exposure in the Altermark mine was more than one order of magnitude below that in the Selevan et al. [1979] study (0.12–1 WL), supporting the hypothesis that the difference in lung cancer incidence could be related to a difference in radon daughter exposure. The Norwegian miners we studied had a high proportion of ever smokers; thus smoking habits cannot explain the difference in lung cancer incidence between the miners in the two cohorts.

The probability of detecting an increased lung cancer incidence during the follow-up period in this study ($\alpha = 0.05$, one-sided), assuming a Poisson distribution, is 65% for a true RR = 2.0 and 97% for RR = 3.0.

CONCLUSIONS

The present study does not confirm an association between lung cancer, morbidity or respiratory disease mortality and exposure to non-asbestiform talc with low quartz content in the one mine and one mill we studied. Further follow-up time is needed to lessen any impact of "healthy worker" selection.

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